REMARKS

Amendments to the claims

Claims 1, 20, 32, 40 and 41 are amended herein without any intent of disclaiming equivalents thereof. Claims 5 and 10 are canceled herein without prejudice to Applicant's right to pursue their subject matter in this application or in related applications.

Claims 1, 20 and 32 are amended to specify that the first biological parameter and the second biological parameter each comprises one of total hCG, PAPP-A, Inhibin-A, AFP and uE_3. Support for the amendments to claims 1, 20 and 32 can be found at least at original claims 5 and 10. Claims 40 and 41 are amended to recite a correlation coefficient greater than 0.6. Support for the amendments to claims 40 and 41 can be found at least at original claims 4 and 9. Applicants submit that the amendments to the claims introduce no new matter. Upon entry of this amendment, claims 1-4, 6, 8, 9, 11, 12, 14-20, 22, 23, 25-27, 32, 40, and 41 will be pending and presented for examination.

Claim Objections

Claim 1 was objected to because abnormality was misspelled. Applicants amend claim 1 to correct the spelling of abnormality. Applicants request reconsideration and withdrawal of the objection.

Rejections under 35 U.S.C. §101

Claims 1-4, 8-9, 14-17, 19-20, 22-23 and 25-27 stand rejected under 35 USC §101 as allegedly being directed toward non-statutory subject matter. Applicants note that neither claim 5 nor claim 10 was rejected under 35 USC §101 as being directed toward non-statutory subject matter. Applicants amend independent claims 1 and 20 to incorporate the specific biological parameters including one of total hCG, PAPP-A, Inhibin-A, AFP and uE_3 from dependent claims 5 and 10.

Applicants traverse the rejection to the extent it is maintained over independent claims 1 and 20, as amended. Claims 1 and 20 are drawn to methods for using biological parameters (e.g., biological markers) to generate likelihood ratio data for determining the likelihood of an at-risk pregnancy. Specifically, the assayed levels of physical substances—biological parameters

including one of total hCG, PAPP-A, Inhibin-A, AFP and uE_3—are measured in samples from a pregnant woman, and the measured levels are then converted into likelihood ratio data from which the probability of an affected fetus can be determined. Thus, at least one material transformation occurs: converting a tangible amount of a biological parameter including one of total hCG, PAPP-A, Inhibin-A, AFP and uE_3 into likelihood ratio data. Moreover, even if the Examiner considers the measured biological parameter levels to be non-physical information, this information is still transformed into a materially different thing in the form of risk likelihood data, such as a risk assessment table. Applicants therefore submit that amended claims 1 and 20 are directed to statutory subject matter, as are claims 2-4, 8-9, 14-17, 19, 22-23 and 25-27 which ultimately depend from claims 1 and 20. Accordingly, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103

Claims 1-6, 8-12, 14-20, 22, 23, 25-27, 32 and 40-41 stand rejected as unpatentable over European Patent No. EP 0 800 085 to Davies ("Davies") in view of International Publication No. WO 99/56132 to inventor Wald by agent Nicholls ("Nicholls").

Davies discloses a method for prenatal screening for Down's Syndrome by calculating a single normalization value of one parameter. In the method disclosed by Davies, the level of hCG or the free alpha or beta subunit thereof is measured at a first and second week and the level at the second week is divided by the level at the first week to form a normalized value. This normalized value is compared to populations of women with and without Down's Syndrome affected pregnancies and deviations determined. That is, Davies measures the value of a single marker at two time points during a pregnancy and uses the values from the two time points to form a single normalization value which is compared to populations of normal and Down's Syndrome pregnancies.

Nicholls discloses a method for prenatal screening for Down's Syndrome by calculating a single value for two or more markers, each maker calculated at a different stage of pregnancy. In the method disclosed by Nicholls, a first marker is measured once in the first stage of pregnancy and a second marker is measured once in the second stage of pregnancy. The single value for each of the two markers is compared to reference data of populations of women with and without Down's Syndrome affected pregnancies.

In contrast, in each of Applicants' independent claims 1, 20 and 32, *two* biological parameters are measured at *two* points in time and feature vectors are constructed using the median values of the parameters and a ratio of the two feature vectors is used to determine likelihood ratio data. That is, in the present invention, *two different markers are each measured at two stages*. The values of each marker are compared with a predicted value at each of two stages to determine *four* multiple of median values (one for each marker at each stage). Applicants submit that the vector analysis of the claimed invention, obtained by measuring at least two markers over at least two time points, provides a test that is more predictive than the sum of the Davies test and the Nicholls test.

Applicants' claimed invention appreciates that it is advantageous to measure markers which are highly correlated with one another at two different gestational ages, because this enables some degree of compensation for natural variations in a marker between subjects. Because Applicants' claimed invention makes repeated measurements of the same biological marker at different stages, the method enhances the test's discriminatory power and, for a given detection rate, reduces the false positive rate as compared to the tests of either Davies or Nicholls. Additionally, in contrast to either Davies or Nicholls, Applicants' claimed invention can make use of markers that have predictive value at one stage of pregnancy but not at another, further reducing the false positive rate. Indeed, Nicholls teaches against the use of highly correlated markers broadly, because one would expect markers which are correlated with one another to provide little new information.

For example, Davies combines two measured values to form a normalized value C and, in order to be predictive, the marker used must discriminate clearly from the normal (i.e. above 50%) at one stage but not from the normal (i.e. below 20%) at the other stage. In contrast, in Applicants' claimed invention, each of the "standardized" measured values are individually included in a feature vector. Thus, the discriminatory information from each individual measurement of each marker over time is retained. Accordingly, Applicants' methodology is applicable to markers which discriminate either at both stages of pregnancy or only at one stage. For example, PAPP-A is discriminatory in both the first and second stages and thus it is more effective to use the methodology of the present invention to incorporate both measurements of PAPP-A than the methodology of Davies, in which the two measurements of PAPP-A are

combined into a single value C, or the methodology of Nicholls, in which a single measurement of PAPP-A is obtained at a single time point.

Accordingly, for at least the reasons given above, Applicants submit that independent claims 1, 20 and 32, and the claims that depend therefrom, are patentable over Davies and Nicholls, either alone or in combination.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance and therefore request early favorable action by the Examiner.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

Respectfully submitted,

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